MEETING REPORT

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Alzheimer’s Disease: Scientific Progress for Future Trends


ALZHEIMER’S DISEASE (AD) is a major problem of health in developed countries, along with cardiovascular disorders, cancer and AIDS, affecting approximately 3%–10% of people older than 65 years of age. This neurodegenerative process is becoming an alarming socioeconomic and biomedical problem due to its high costs for society as well as to management difficulties for the medical and scientific community in terms of etiopathogenesis, diagnosis and treatment. At the International Workshop on Alzheimer’s Disease: Progress for the Next Decade held in Madrid, Spain, on March 22–23, 1993, under the auspices of the Ramón Areces Foundation, the authors of this article, from Europe, the U.S. and Japan, tried to pose, from a multidisciplinary approach, the most important questions related to AD on the basis of present knowledge in order to bring some new insights into the nature of this devastating disorder. Each of the following sections details the relevant questions for that aspect of the disorder.

Etiopathogenesis

Is AD a monofactorial problem? Are early-onset AD and late-onset AD the same disorder? Are paired helical filaments/neurofibrillary tangles (PHF/NFT) and β-amyloid deposition interrelated processes? Are PHF/NFT and/or β-amyloid fundamental for the phenotypic expression of AD? Is AD a genetic disease? Which are the most relevant risk factors for AD?

Diagnosis

Are the present diagnostic tools appropriate for the early diagnosis of AD? Are the current clinical criteria for AD adequate for the medical community? Are data provided by clinical symptoms, neuropsychological assessment, neuroimaging and neurochemistry reliable enough for the early diagnosis of AD? Can we rely on biological markers for diagnosing AD? Which is the most suitable diagnostic strategy for the early diagnosis of AD? Which are the most suitable neuropathological markers for AD?

Treatment

What is the therapeutic value of the present palliative treatment? What are we obtaining with substitutive treatments? How should conventional psychopharmacology be managed in AD? What is the future of neurotrophic factors in AD treatment? What is the potential utility of neuroimmunomodulators as a therapeutic strategy in AD? How should an etiopathogenic treatment be addressed in AD?

Two days of discussions demonstrated that in the past decade we have obtained a considerable amount of data on AD, with controversial results in some respects, particularly related to etiopathogenic factors. However, most of our apparently contrasting postulates at present may become complementary

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facts in the near future. In this regard, most authors agree on the following conclusions.

Conclusions

1. Alzheimer’s disease is a heterogeneous syndrome in nature.

2. Early-onset familial AD (FAD) may be caused by several genes which operate as simple autosomal dominants, including alterations in chromosome 14 (in 84% of cases of early-onset FAD) and APP mutations in chromosome 21 (in 15% of cases with early-onset FAD).

3. Late-onset AD is likely to be caused by oligogenic inheritance (due to several genes, some of which may map on chromosome 19), by polygenic factors and/or by environmental factors leading to phenocopies.

4. From recent epidemiological studies (EURODEM Project), we can conclude the following: a) the prevalence of dementia increases from one in 100 at the age of 60 years to one in three at the age of 90 years; b) Alzheimer’s disease accounts for about two out of three dementia patients; and c) risk factors for Alzheimer’s disease are: positive family history of dementia, Down’s syndrome, Parkinson’s disease, history of depression and head trauma. Smoking may be inversely related to the occurrence of Alzheimer’s disease.

5. Normal aging of the brain involves shrinkage of neocortical large neurons and decrease of synapses, and Alzheimer’s disease involves loss of large cortical neurons and loss of synapses, showing that normal aging and AD are additive in these regards.

6. β-Amyloid is a critical molecule in the development of Alzheimer’s disease.

7. Cells making amyloid were identified as brain reticuloendothelial cells of the microglial type. These cells may be involved in neuroimmune processes and should be attenuated or killed to stop the formation of amyloid deposits that destroy the brain tissue through different mechanisms, some of which may be associated with neuroimmune processes.

8. Cytoskeletal changes and synaptic loss are crucial to the phenotypic expression of AD.

9. The histological hallmarks of AD are the fibrous protein deposits in the form of the intracellular neurofibrillary tangles (NFT), the extracellular β-amyloid and the synaptic loss present in AD brains.

10. The β-protein, which is making fibrils, and Tau protein, which is engaged in the formation of NFT, are host proteins that turn from readily soluble proteins into difficult-to-solubilize proteins owing to changes in conformation from α to β proteins.

11. The deposition of β-amyloid alone, in the absence of neurofibrillary changes, may not be enough to produce the clinical expression of AD.

12. The presence of neurofibrillary changes in the presence or absence of β-amyloid may induce the clinical expression of AD.

13. Microtubule-associated protein Tau is the major protein subunit of PHF in NFT.

14. Tau protein in AD brains is abnormally phosphorylated.

15. Abnormal phosphorylation of Tau precedes the formation of NFT.

16. Abnormal phosphorylation of Tau in AD is a product of a protein phosphorylation/dephosphorylation system defect in the affected neurons.

17. Abnormal phosphorylation of Tau leads to the breakdown of the microtubule system and consequently neuronal dysfunction and degeneration.

18. The injection of cyclosporin A, a calcineurin inhibitor, into the rat brain causes accumulation of neurofilaments in hippocampal neurons, which may constitute a model to study phosphorylation/dephosphorylation processes in neurons.

19. Buffy coat from patients with familial or nonfamilial AD, regardless of the absence or presence of a Hardy-type mutation, produces intracytoplasmic accumulation of phosphorylated, ubiquitinated neurofilaments.

20. This pathological accumulation of neurofilaments can be transmitted in rodents by inoculation of brain homogenerate, and the pathogenic factor is in the platelet fraction.

21. The strongest correlation with cognitive decline is synapse loss in frontal cortex.

22. The strongest correlation of memory function is the number of tangles in the basal nucleus.

23. The extent of neuropil destruction is proportional to the amount of amyloid deposited.

24. Environmental factors acting through APP metabolism (heavy metals, cations, free radical generators) may cause some cases of AD.

25. The activation of a neuroimmune cascade in neurons expressing abnormal epitopes on their membrane may accelerate neurodegeneration and cell death in AD.

26. Neurotransmitter changes in AD may be only an epiphenomenon of the underlying neurodegenerative process occurring in specific neuronal pathways.

27. Changes in the hypothalamus may be responsible for some specific symptoms in AD.

28. In AD, in addition to neurodegeneration, there is an activation of several neurotransmitter systems, including some neuropeptides and neuroimmunomodulators, like IL-1 and brain histamine.
29. Cell death might be an overestimated phenomenon in AD.

30. The main potential functions of APP in the CNS may include membrane receptor activity involved in cell-cell and cell-matrix interactions, signals for cell growth and attachment, regulation of cell growth and neurite extension and modulation of NGF-induced neurite outgrowth.

31. Several experimental models to study APP metabolism may help to understand APP pathology in AD.

32. The mean age of the crystalline-β-amyloid deposits is about 30 years.

33. For clinical research in AD, several important domains of assessment are essential: a) performance-based evaluation of cognition; b) global staging; c) assessment of functional impairment; and d) noncognitive behavioral symptoms evaluation.

34. Early diagnosis is essential in AD. This early diagnosis can be achieved by the combination of clinical data, neuropsychological assessment, neuroimaging, brain mapping, neurochemistry and biological markers with a high accuracy (>95%). The diagnosis of AD relying only on clinical data may induce about 10%-20% of diagnostic errors.

35. The final diagnostic confirmation of AD is neuropathological.

36. Some molecular and genetic markers are under development and may be used as antemortem markers in the future.

37. Determinations of APP in plasma and/or CSF might be a potential antemortem marker for AD.

38. The early treatment of AD with a multifactorial therapy (nootropics, va-saline donors, choline donors, cholinesterase inhibitors, neurotrophic factors) may be the most appropriate therapeutic approach at the present time. Anxiolytics and neuroleptics should be given with caution, because these agents potentiate cognitive deterioration.

39. Basically, three different therapeutic strategies are potentially available: a) a palliative treatment; b) a sub- stitutive treatment; and c) an etiopathogenic treatment. The efficacy of palliative and substitutive treatments in combination is still poor, but clinically important. There are some new expectations with cholinesterase inhibitors, neurotrophic factors and neuroimmunomodulators.

40. The definitive treatment for AD may be possible when the etiology of this disorder is established; however, at the present time a nihilistic attitude concerning the pharmacological treatment of AD is not justified.

41. It is likely that the best therapeutic approach to AD may be multifactorial controlling β-amyloid deposition, inhibiting cytoskeletal changes and stimulating synaptic formation. In any case, the combination of molecular pharmacology together with special programs for somatosensory stimulation and psychosocial support is the best therapeutic strategy for AD patients.

CANGENE ACQUIRES RIGHTS TO NEEDLE-FREE DRUG DELIVERY SYSTEM

Cangene Corp. announced April 21, 1993, that it has acquired the exclusive global rights to market a needle-free drug delivery system from the Medi-Ject Corp. of Minneapolis, Minnesota, U.S.A., for a range of drugs being developed by Cangene. The two companies will negotiate a formal licensing agreement relating to the delivery system upon successful completion of modifications to the prototype required by Cangene.

"The device is simple for any patient to use and completely painless," said James M. Rae, Vice President of Marketing at Cangene. "By enabling patients to self-administer drugs at home and reducing hospital visits, it should reduce treatment costs. By reducing pain and anxiety to patients, it will help ensure that the treatment is followed completely."

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